REMARKS

Claims 1-3, 8-11 and 25-30 are now pending in the application. Claims 25-30 are new.

I. Restriction Requirement

Restriction of claims 12-24 has been made final over applicant's traverse. Without acquiescence in the reasoning of the Restriction Requirement, the previously withdrawn claims have been cancelled to advance prosecution. Applicant reserves the right to file a divisional application on the subject matter.

II. Indefiniteness Rejections

Claim 1 has been rejected as indefinite as incomplete for failing to specify a subject of the administration. The claim has been amended and now specifically recites a subject. Withdrawal of this rejection is requested.

Claim 2 has been rejected as indefinite for use of "associated with" without definition in the claim. The claim has been amended to refer to the antecedent skin disorder specified in claim 1. Withdrawal of this rejection is requested.

It is noted that the term "associated with" also appears in new claim 25. In claim 25 the term is used to identify kind of receptor-binding specificity and is not seen to raise the same issue presented in original claim 2.

Claim 7 has been rejected as indefinite for use of "rapid." Claim 7 has been cancelled, mooting the rejection.

III. Anticipation Rejection

Claims 1-8 have been rejected under 35 U.S.C. 102(e) as being anticipated by *Beachy et al* (US 6,432,970). The rejection is traversed.

The factual determination of anticipation requires the disclosure in a single reference of every element of the claimed invention. *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999); *In re Lowry*, 32 USPQ2d 1031 (Fed. Cir. 1994); *Continental Can Co. USA Inc. v. Monsanto Co.*, 20 USPQ2d 1746 (Fed. Cir. 1991); *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990); *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 7 USPQ2d 1315 (Fed. Cir. 1988); *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978); *In re Arkley*, 455 F.2d 586, 172 USPQ 524 (CCPA 1972). Anticipating prior art must enable the invention. In particular, one must be able to make the claimed invention without undue experimentation. *Minnesota Mining and Manufacturing Co. v. Chemque Inc.*, 64 USPQ2d 1270 (CA FC 2002; *In re Donohue,* 766 F.2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). Even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. *In re Borst,* 345 F.2d 851, 855, 45 USPQ 554, 557 (CCPA 1965), *cert. denied,* 382 U.S. 973, 148 USPQ 771 (1966.)

Beachy et al is an omnibus disclosure pertaining to a "subject method" which is said to be the administration of a subject antagonist or agonist of Hedgehog (Hb) signaling onto cells *in vitro* or in *vivo.* Reading the document as a whole it is apparent that it is nothing but a proposal for research. The exemplification portion of *Beachy et al* has no instance of a therapeutic effect (see cols 57-62). The rest of the disclosure is simply speculation as to a variety of conditions that might be influenced by the subject compounds. Many of the statements are self-contradictory or teach away from the invention claimed in the present invention.[1]

Unlike the present application, in *Beachy et al* there is no demonstration of a therapeutic effect of *any kind* with any of the compounds in *any subject.*

Both independent claims 1 and 25 recite administration of a sufficient amount of the medicament that induces differentiation of epidermal cells in lesional skin and the regression and/or disappearance of skin lesions. Claims 1 and 25 are not anticipated at least because such an *amount* is not anticipated.

The Office Action cites col. 41, lines 43-57 of *Beachy et al.* The cited section is refers to an "antiproliferative embodiment." This statement leaves it to the reader to work out which compound is to be used and what amount of medicament is to be used to produce the therapeutic result. This is a classic case of undue experimentation. As for the therapeutic result itself, inhibition of proliferation is what is contemplated in the *Beachy et al* teachings.[1] Thus this proposal, whatever its specifics may be, is not a disclosure of a process wherein a sufficient amount of a medicament is administered to induce regression and/or disappearance of the lesions.

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[1] A more detailed discussion of the Beachy et al disclosure including identification of such self-contradictions as it pertains to the claimed invention is in Appendix A.

It is a fact that *inhibition of proliferation does not necessarily induce differentiation.*[2] Thus, even if *Beachy et al* were considered as an enabling teaching of the use of an *antagonist* of Hh signaling to inhibit proliferation in psoriatic lesions, it does not anticipate the presently claimed invention.

The present application describes a clear dose-dependent effect of cyclopamine on the regression of psoriatic lesions. Besides the description of medicament applications for different durations, design of the described investigations entails administrations of medicament onto only a half of a psoriatic plaque followed by the excision and analyses of entire plaque. In such an approach, the half of the lesion onto which cyclopamine is not directly applied receives a relatively lower dosage of cyclopamine by diffusion from the adjacent half. This allows determination of the effects of varying concentrations of cyclopamine *in vivo* on psoriatic lesions. As stated on page 20, lines 1-5, and exemplified in Figures 2E, 2F, the regions of psoriatic lesional skin that receive relatively lower concentrations of cyclopamine display the morphological signs of regression towards normalcy relatively less pronouncedly (compare also with Fig. 2C and 2.D). In particular, the specification describes dose-dependence of the inhibition of proliferation of epidermal cells and shows that *a dosage of cyclopamine that causes significant inhibition of proliferation is insufficient to cause normalization of the morphological signs of psoriasis* (see page 20, line 22 to page 21, line 5 and Fig. 2J; compare also with Fig. 2H and with Fig. 2I). On the other hand, the half of the same lesion receiving a sufficient dosage of cyclopamine is shown to become almost indistinguishable from the non-lesional skin by morphological criteria (see Fig. 2I and 2K). Other photomicrographs of the tissue sections showing the junctional area between the cyclopamine-applied and non-applied lesion halves (e.g. Fig. 2O, Fig. 2W) show again a clear dose-dependent effect of cyclopamine. Further analyses of the effects of varying doses of cyclopamine on psoriatic lesions also confirm the dose-dependent regression of psoriatic lesions and demonstrate that a suboptimal dosage of cyclopamine would fail to provide clearance of lesions and an initially regressed lesion may even reprogress if an insufficient dosage is applied [see page 26, line 13 to page 27, line 19 and Table 1 (page 31, line 1 to page 32, line 4)]. It is thus clear that a minimum dosage of cyclopamine that is sufficient to provide inhibition of proliferation of epidermal cells in psoriatic lesional skin is not sufficient to provide the therapeutic outcome recited in claims 1 and 25.

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[1] See Appendix A, headings 2 and 3

[2] See Appendix A, heading 3.

Beachy et al further teach that a minimum dosage which will produce a therapeutic effect is to be used (column 44, lines 14-24; "*... start ... at levels lower than that required ... and gradually increase the dosage until the desired effect is achieved." "In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect.")*. Following this teaching the skilled person seeking inhibition of proliferation does not employ a dosage which produces remission or disappearance of the lesion.

Regarding the rejection of claims 8-10, the applicant also traverse the mistaken statement on page 4 of the September 14, 2006 Office action that *Beachy et al* teach co-administration of a corticosteroid and a steroidal alkaloid inhibitor of Hh signaling at col. 28 lines 40-55. This location speaks of using a steroidal alkaloid which does not interfere with biological activity of a list of steroids. It does not teach to administer such steroids with a steroidal alkaloid. Moreover, the *Beachy et al* teach away from such a co-administration and state that a subject antagonist of Hh signaling is to lack a specific or significant binding to a member of the nuclear hormone receptor superfamily and to lack in this manner biological activity and unwanted side effects that may arise from corticosteroid administration (see column 28, line 36 to column 29, line 9). Well-known effects of prolonged or high-dose corticosteroid administrations, e.g. hyperglycemia, muscle wasting, hypertension, increased susceptibility to infections, Cushinoid features are listed and a subject Hh antagonist is said to preferably avoid these (see column 28, line 67 to column 29, line 9). Thus *Beachy et al* do not anticipate co-administration or sequential administration of a corticosteroid and a Hh signaling antagonist and do not anticipate a medicament comprising of a corticosteroid and Hh signaling antagonist.

For the reasons given above the subject matter of the currently presented claims is not anticipated by *Beachy et al.* Withdrawal of the rejection is respectfully requested.

IV. Obviousness Rejections

Claim 9 has been rejected for obviousness over *Beachy et al* in view of *Busse et al* US 4,370,322. The rejection is traversed. For the reasons already given *Beachy et al* does not teach an administration which meets the recitations of claims 1 and 8, and further leads away from co-administration of the described steroidal alkaloids in combination with a corticosteroid. As it pertains to the subject matter of the claims of the present application *Beachy et al* is nothing more than an *invitation to experiment* with hedgehog antagonists as a class. It is well established that an obviousness rejection cannot be maintained on an "obvious to try" standard. *In re Fine,* 5 USPQ2d 1596 (Fed. Cir. 1988). *Busse et al* does not provide a teaching which meets the deficiencies of the *Beachy et al* patent.

Furthermore, as the Applicant details in Appendix B there is substantial objective evidence of non-obviousness. The use of a specific inhibitor of Hh signaling for inducing differentiation of epidermal cells was not inherent in the prior art and is a surprising result. Further the attainment of described therapeutic efficacy was highly unexpected. In particular, in the treatment of psoriatic lesions the method has substantial benefits relative to alternative treatments. Still further, regarding the sequential or co-administration of a corticosteroid with a Hh signaling inhibitor, not only does the prior art teach away from such co-administration, the experimental results described in this application show a clear *synergistic* effect of the described combination. There is no basis in the prior art to expect such a result.

For the foregoing reasons withdrawal of the obviousness rejection of claim 9 is requested.

Claim 10 has been rejected for obviousness from *Beachy et al.* For the reasons already given *Beachy et al* does not teach an administration which meets the recitations of claims 1 and 8, and specifically teaches to stop when the expected therapeutic result is observed. This technique specifically precludes a dosage as claimed since the antiprolifferative effect is observed at a lesser dosage than lesion regression. At best, *Beachy et al* is an invitation to experiment. Moreover the secondary considerations just mentioned also pertain to claim 10. Withdrawal of the rejection of claim 10 is requested.

V. Provisional Obviousness-Type Double Patenting Rejection

Claims 1 and 2 have been provisionally rejected as being unpatentable over claims 1-5 and 10-12 of co-pending Application No. 10/682584 in view of *Beachy et al* (US patent 6,432,970). Reconsideration is requested.

As of the date of this amendment, the currently presented claims of the present application are directed to a treatment method for a non-tumoral skin disorder. The currently presented claims of Application No. 10/682584 are directed to a treatment method for tumor cells. A clean line of distinction is therefore provided. The deficiencies of *Beachy et al* have been stated above. A skilled person would not find the subject matter of the present claims obvious from the claims of 10/682584 taken with *Beachy et al.* Withdrawal of this rejection is respectfully requested.

VI. Conclusion

In view of the foregoing amendments and remarks, the outstanding rejections are seen to be overcome. Accordingly, withdrawal of the outstanding rejections and allowance of the application is respectfully requested.

Respectfully submitted,

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Appendix A
Review of *Beachy et al*

1. Subject Method

Beachy et al refer frequently to a "subject method." This is a ***profoundly ambiguous*** term. In some embodiments *Beachy et al*'s subject methods involve administration of an antagonist of Hedgehog (Hb) signaling onto cells *in vitro* or in *vivo* (see e.g. col. 37, lines 37-41), but in other embodiments they involve administration of a Hedgehog *agonist* (see e.g. col. 37 lines 42-45). *Beachy et al* also disclose a long list of highly heterogenous conditions, including conditions that are poorly defined or undefined (see e.g. column 8, lines 34-49; "regulation of lung, liver ... etc"), as being treatable by use of said method. Moreover the subject methods often involve use of a "subject compound." This term is completely open ended. While *Beachy et al* indicate that certain embodiments involve subject compounds of specific formulas or properties, other embodiments are apparently not so limited. Therefore whenever a method is said to involve a "subject compound" ambiguity reigns both as to which compounds are to be used and what effect may be expected unless a specific clarification is provided (or can be inferred from the specific context).

Even when a clarification is made, or can be inferred, that an antagonist of Hh signaling is to be employed rather than a hedgehog agonist, there is no enablement in writing down the names of highly varying conditions as being treatable by use of such antagonist. It is clear to a person skilled in the art that attainment of a therapeutic effect is inherently unfeasible in entire categories of disclosed conditions. For example, it has been well known that *even a specific inhibitor of Hh signaling can have very different consequences in different tissues of an animal, e.g. on cellular proliferation or epithelial hyperplasia.* Thus, a targeted deletion of the Sonic hedgehog (Shh) gene resulting in inhibition or loss of Hh signaling causes marked hyperplasia in the epithelium of stomach *(Ramalho-Santos M et al, Development* 2000;127:2763-2772)[1] and of joined esophagus-trachea while causing hypoplasia in the lung epithelium *(Litingtung Y et al, Nature Genetics* 1998;20:58-61)[2]. More directly, *van den Brink GR et al (Gastroenterology* 2001; 121:317-328)[3] have described that administration of a specific inhibitor of Hh signaling (cyclopamine) systemically to mice caused marked stimulation of the proliferation of gastric epithelial cells while causing in the same animals an inhibition of proliferation of the intestinal epithelial cells. *Suzuki H et al (Journal of Pathology* 2005;206:186-197)[4] have confirmed with analyses of normal and diseased gastric mucosa that a decrease or loss of Shh in the gastric mucosa leads to a marked hyperproliferative condition.

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[1] Highlighted copies of the references numbered in brackets herein are attached.

2. *Inhibition of Cellular Differentiation by Hedgehog Antagonists is Taught*

Cellular differentiation is said in *Beachy et* al to be "affected" or "altered" or "changed" or "controlled" or "regulated" by a subject compound (see e.g. column 9, lines *8*-15*;* column 29, lines 34-38; column 30, lines 3-4; column 30, lines 14-18; column 32, lines 4-8; column 33, lines 56-61). The preponderance of such unspecific verbs emphasizes the uninformative nature of related teachings. The disclosures concerning the effects of subject Hh signaling antagonists on differentiation of epithelial cells are in addition directly self-contradicting. Thus, it is stated on column 41, lines 43-51 that a hedgehog antagonist can be used to induce differentiation of said cells and it is stated on column 39, lines 10-15 that a hedgehog antagonist can be used to inhibit differentiation of epithelial cells. These ambiguous and self-contradicting disclosures have no utility to the skilled person. Similarly, the cited teaching of *Beachy et al* that "An effective amount of... a hedgehog antagonist ... brings about ... a change in the rate of cell proliferation and/or state of differentiation of a cell" (column 9, lines 8-15*)* may mean a change in the direction of inhibition or in the direction of induction of a differentiated state and therefore lacks utility to a person skilled in the art.

Beachy et al does have teachings relating to Hh signaling on cellular differentiation which are based on the results of experiments described in *Beachy et al* or in the scientific publications cited therein. These teachings taken as a whole lead to the conclusion that the use of Hedgehog antagonists will inhibit cellular differentiation.

The Hh family of proteins were discovered originally as inducers of differentiation of various cell types during development. An inhibition of Hh signaling would thus ordinarily be expected to act to inhibit said differentiation events. Table 1, below, shows that the experimental findings that are described in *Beachy et al* concerning the effects of Hh signaling on the differentiation of various cell types commonly point to an inhibitory action of Hh signaling antagonists on differentiation.

Table 1. The Supported Teachings In *Beachy e al* That Teach Away From The Use Of Cyclopamine Or Another Specific Inhibitor Of Hedgehog Signaling For Induction Of Cellular Differentiation

Column and Lines	Teaching
Col. 2, lines 62-63	"...Shh...induce ventral cell fates" (references are given)
Col. 3, lines 4-12	"...Shh protein induces floorplate and motor neuron...antibody blocking suggests that Shh...is required for...induction of motor neuron fates" (references are given)
Col. 3, lines 9-29	"...filter barrier experiments suggest that Shh mediates the induction of sclerotome directly" (reference is given)
Col. 5, lines 9-29	Referring to Fig. 3, describes induction of the floor plate and motor neurons by Shh and states that said inductions of differentiation are fully inhibited by sufficiently high concentrations of cyclopamine or jervine.
Col. 6, lines 22-49	Referring to Fig. 6, describes induction of the floor plate and motor neurons by Shh-N protein and states that said inductions of differentiation are "completely blocked" by sufficiently high concentrations of cyclopamine or jervine.
Col. 39, line 65 to Col. 40, line 2	"...lhh...promote...photoreceptor differentiation" (reference is given)
Col. 40, lines 3-10	"...treatment...with...Sonic hedgehog protein results in an increase in...rod photorecptors, amacrine cells and Muller glial cells (reference is given)
Col. 58, lines 12-19	"...cyclopamine and jervine...a complete loss of HNF3ß and lsl-1 expression consistently causes by sufficiently high concentrations"
Col. 60, lines 4-17	"...Shh-N protein...induces ventral markers such as lsl-1 and HNF3ß...teratogenic compounds are able to block...induction of lsl-1 and HNF3ß"
Col. 62, line 66 to Col. 63, line 2	"We have...demonstrated that these compound block the induction by Shh protein of ventral cell types"

Beachy et al also state that "*in light of the ... broad involvement of hedgehog proteins in the formation of... differentiated tissues in vertebrates,*" the use of Hh proteins is contemplated for the generation of various vertebrate tissues in general (column 29, lines 39-45). Thus, what is shown experimentally and what is contemplated is the induction of differentiation of various vertebrate cell types by use of Hh signaling agonists and it is described that said differentiation events are *inhibited* by Hh signaling *antagonists.*

3. "Antiproliferative" does not Teach an Induction of Differentiation

By reference to the prior art publications that describe a stimulation of cellular proliferation by Hh signaling and the inhibition of said proliferation in response to a specific inhibitor of Hh signaling (e.g. column 35, lines 41-59), *Beachy et al* state that a subject antagonist of Hh signaling can be used for treating disorders associated with increased proliferation (see column 35, lines 41-59; column 39, lines 23-26; column 40, lines 2-12). Only by inference from these statements can the reference to an "antiproliferative embodiment" at col. 41, lines 43-57 be taken even as pertaining to use of a hedgehog antagonist.

As set forth under the heading 2, above, *Beachy et al* teaches that use of hedgehog antagonists will inhibit differentiation. *Beachy et al* does not show a different result in connection with the "antiproliferative" embodiment.

Relating to proliferation, hedgehog antagonists are said by *Beachy et al* to exert an inhibition of proliferation effect and to lack a cell-killing effect ["because a hedgehog antagonist will often be cytostatic to epithelial cells, rather than cytotoxic, such agents can be used ... (for) inhibiting the cells from entering S phase, and thereby preventing ... programmed cell death" column 40, lines 57-67]. Therefore an inhibition of proliferation appears to be what is desired in terms of the therapeutic effect.

Hh signaling had been described in prior art to stimulate proliferation of a number of cell types and an inhibition or removal of Hh signaling was found to inhibit proliferation (see e.g. *Basler K et al, Nature* 1994;368 :208-214[5]; *Heberlein U et al, Nature* 1995;373 :709-711[6]; *Oro AE et al, Science* 1997;276:8 17-821[7]; *Fujita E et al, Biochemical and Biophysical Research Communications* 1997;238:658-664[8]. *Beachy et al* also refer to some of these prior art publications. These publications do not show that induction of differentiation was recognized to be an inherent consequence of inhibition or removal of Hh signaling.

Further, *an inhibition of proliferation effect does not necessarily cause induction of differentiation.* It is now well-established that induction of differentiation of many cell types requires proliferation of the cells for at least one or more cell cycles (the replication-associated remodeling of chromatin appears to be a fundamental reason behind this requirement of proliferation for differentiation; see e.g. *Fisher D e t al, EMBO Journal* 2003;22:3737-3 748)[9]. Experiments with the epidermal keratinocytes also show that *proliferation of epidermal cells can be inhibited without inducing their differentiation.* Moreover, certain inhibitors of proliferation (e.g. TGF-ß) prevent the induction of differentiation by known inducers of differentiation (see *Bollag WB et al, BMC Pharmacology* 2004; 4:13)[10].

Beachy et al teach also that a minimum dosage that will produce a therapeutic effect is to be used (column 44, lines 14-24;"*... start ... at levels lower than that required ... and gradually increase the dosage until the desired effect is achieved." "In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect.").* Consequently the skilled person will not necessarily use an amount of an inhibitor of Hh signaling that induces cellular differentiation in the course of experimentation to find an amount which inhibits proliferation.

Thus, the disclosures of *Beachy et al* of an antiproliferative embodiment and the inference that such embodiment involves use of a Hedgehog signaling antagonist does not equate to a teaching of induction of differentiation.

Appendix B
Objective Evidence of Non-obviousness

Use of cyclopamine or another specific inhibitor of Hh signaling for induction of differentiation of epidermal cells, was unobvious in the prior art to the present invention. As already noted, Hh proteins were well known in prior art as inducers of differentiation of various cell types and *Beachy et al* also refer to said effects. The prior art as a whole was also teaching away from the use of cyclopamine or another specific inhibitor of Hh signaling for inducing differentiation of epidermal cells. Specifically with regard to the differentiation of epidermal cells, prior art had described the Hh proteins as inducers of cellular differentiation and, further, epidermal cellular differentiation was described to occur normally in the skin showing stimulation of epidermal cellular proliferation in response to an upregulation of Hh signaling (see Table 2 below).

Table 2. Prior Art Specifically Teaches Away From The Use Of An Inhibitor Of Hedgehog/Smoothened Signaling For Induction Of Differentiation Of Epidermal Cells

Document	Teaching
Stone DM et al, *Nature* 1996; 384: 129-134[11]	"...the Hh system may provide...differentiative signals to basal cells in the skin throughout the life...With a receptor for Shh (and Dhh) identified, it will now be possible to study the mechanisms by which the Hh family exerts mitogenic, differentiative and morphogenic effects"
Struhl G et al, *Development* 1997; 124: 2143-2154[12]	Hh protein acts to specify cuticular structures that differentiate from the epidermal precursor cells.
Oro AE et al, *Science* 1997; 276: 817-821[7]	Skin tissue displaying increased epidermal cellular proliferation because of the activation of Hedgehog/Smoothened signaling shows immunohistochemical findings that are "*consistent with the normal differentiation pattern of stratified epithelium*"
Maesawa C et al, *Genes Chromosomes Cancer* 1998; 21: 276-279[13]	Activation of Hedgehog/Smoothened signaling "could provide...differentiation signals to basal cells in the skin"

Therefore, the use of a specific inhibitor of Hh/Smo signaling (cyclopamine) for inducing differentiation of epidermal cells was highly unexpected in prior art.

The technical effects and therapeutic results described in the present application were unexpected and surprising also for several other reasons.

1) A recently issued US patent filed before the priority date of the present application discloses the use of a modulator of Hh signaling for treatment of psoriasis. This patent describes the effects of hedgehog proteins (and agonists thereof) on immune system cells and, on the basis of said effects, suggests the use of such proteins or agonists, *i.e. upregulators* rather than inhibitors, of Hh signaling for treatment of psoriasis (see the US 6,951,839, column 7, lines 29-37). The patentee of US 6,951,839 was specifically aware of apparently related US patent applications of Beachy (see col. 46, lines 30-36) and the proprietor of US 6,951,839 is the same as that of US 6,291,516, which has largely overlapping disclosure with that of *Beachy et al* (often identical word-by-word over extended passages).

2) Various specific inhibitors of cellular proliferation were evaluated in prior art for treatment of psoriasis. However, it is well known in art that even the most commonly used inhibitor of proliferation in clinical practice, methotrexate, provides only a partial regression after several weeks of use. On the other hand, the presently described method of treatment has been shown to provide full clearance within a few days. This is a highly surprising and unexpected therapeutic result.

3) Psoriasis has been considered in prior art to be a primarily T-cell mediated disease caused by CD4(+) and CD8(+) T lymphocytes. While many treatments directed specifically to said cells were described in prior art, none of such methods of treatment were found to be as efficacious as the presently described method of treatment (see e.g. *Krueger JG, Journal of the American Academy of Dermatology* 2002;46: 1-23)[14]. The specification of the present application describes clearance of the CD4(+) T lymphocytes and other inflammatory cells from lesional skin within a few days of treatment by use of present method (see page 4, lines 14-18; page 19, lines 21-23; page 22 line 15 to page 23, line 2 and Figures 2B, 2C, 2V, 2W).

4) The present invention describes full clearance of lesions in patients while sparing the normal skin tissue, including the undifferentiated cells displaying progenitor and stem cell features. Both structural and functional evidence are described in this regard (see e.g. page 15, lines 2-3; page 16, lines 16-23; page 22, lines 1-13; page 23, lines 20-28; page 25, lines 1-9; page 30, lines 15-25 and the related figures). Attainment of such a result is unexpected and surprising both because Hh signaling was described in prior art to be essential for the maintenance of stem cells *(Zhang Yet et al, Nature* 2001; 410:599-604) [15]and because the adverse effects on undifferentiated and stem cells were well known to limit applicability of many prior art methods of treatment (see e.g. *Lebwohl M. et al, Journal of the American Academy of Dermatology* 2001; 45:649-661[16] for a general review).

Therapeutic efficacy of a method of treatment depends on the ratio of its therapeutic effects to its toxic/adverse effects. Poor therapeutic efficacy of prior art treatments had led to a multitude of trials for psoriasis treatment. However, it is well known that none of the prior art methods shows a therapeutic efficacy that is comparable to that described in this invention (see e.g. *Al-Suwaidan SN et al, Journal of the American Academy of Dermatology* 2000;42:796-802)[17]. For example, Vitamin D3 and various derivatives/analogs thereof were evaluated in prior art in treatment of psoriasis. Although having some efficacy, said compounds are known to exert unacceptable adverse effects at increased doses, including those on calcium metabolism that are ascribed to the liganded Vitamin D3 receptor. Consequently, even the treatments employing Vitamin D3 derivatives/analogs with a reduced effect on calcium metabolism were well known to be capable providing partial regression after several weeks of treatment (see e.g. the review *of Al-Suwaidan SN et al, ibid).* In contrast, the present method of treatment provides clearance of lesions within a few days. A recent publication that Vitamin D3 can bind to the Smoothened protein besides Vitamin D3 receptor and can act as an inhibitor of Hh signaling *(Bijlsma MF et al, PloS Biology* 2006;4:e232)[18] raises the possibility that the therapeutic effects described in prior art with a Vitamin D3 derivative/analog may in part be due to a (then unrecognized) inhibitory effect on Hh signaling. If so, other prior art studies with Vitamin D3 and related molecules further support the unobviousness of present invention. Thus, *Gniadecki R (British Journal of Pharmacology* 1997; 120:1119-1127)[19] had reported in prior art that Vitamin D3 and a number of derivatives/analogs thereof had effective concentrations (EC50) for inhibition of proliferation of keratinocytes that are only a small percentage of their EC50 for the induction of differentiation of same cells (less than 10% in case of Vitamin D3; about a 12 fold difference). Said findings are in accord with those described in this application that a minimum dosage of cyclopamine that is sufficient to provide inhibition of proliferation is insufficient to provide the presently claimed technical effects and therapeutic outcome. It is also clear that the effective concentration of Vitamin D3, for example, for the induction of differentiation of keratinocytes (EC50 ~ 180 ± 12 nM) is beyond that can be achieved by a systemic administration before being precluded by serious toxic effects (this is well known in art also from the clinical experience with Vitamin D3 overdoses).

5) Concerning the sequential or co-administration of a corticosteroid with a Hh signaling inhibitor or combining the two in a medicament, the prior art was specifically teaching against doing so (explained in response to the anticipation rejection; *Beachy et al,* column 28, line 36 to column 29, line 9; other prior art patent applications were also similarly teaching away, see e.g. US patent 6,291,516, column 35, line 60 to column 36, line 31). Furthermore, the experimental results described in this application show a clear *synergistic* effect of the described combination (see for example the quantitative data in Table 1 of the specification). While it is true that corticosteroids were used in prior art for treating psoriasis, it is far from obvious that a synergistic effect (rather than an additive effect) would be obtained. Particularly since an unprecedented therapeutic efficacy was shown by the method of treatment using cyclopamine, a further (and more than additive) improvement in the rate of clearance of psoriatic lesions is far from obvious. In addition, examples are known that co-administration of a corticosteroid with

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a medicament that is effective in treatment of psoriasis may produce no additional therapeutic benefit at all (see e.g. *Bovenschen HJ et al, Archives of Dermatological Research* 2007; 298:457-463)[20].